

CLAIMS

We claim:

1. A method for preserving antigen presentation on a virally infected mammalian cell, comprising:

Sub. a1 (a) providing a population of mammalian cells at least a portion of which is suspected of being virally infected and

(b) contacting said cells with an anti-apoptotic reagent, thereby preserving antigen presentation on virally infected cells.

2. The method of claim 1, wherein said cells comprise peripheral blood leukocytes.

3. The method of claim 1, wherein said cells comprise neutrophils.

4. The method of claim 1, wherein said cells comprise granulocytes.

5. The method of claim 1, wherein said virus is selected from the group consisting of herpes, HIV, cytomegalovirus (CMV), and hepatitis.

6. The method of claim 5, wherein said virus is CMV.

7. The method of claim 1, wherein said antigen comprises a viral antigen present on the surface of said mammalian cells.

8. The method of claim 7, wherein said antigen comprises pp65 protein of CMV.

9. The method of claim 1, wherein the contacting is *ex vivo*.

~~10. The method of claim 1, wherein the reagent is a nucleic acid.~~

~~11. The method of claim 10, wherein the reagent is an ICE antisense sequence.~~

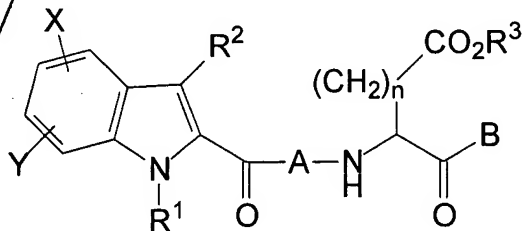
12. The method of claim 1, wherein the reagent is a protease inhibitor.

13. The method of claim 12, wherein the protease inhibitor is irreversible.

14. The method of claim 12, wherein the protease inhibitor is reversible.

15. The method of claim 12, wherein the protease inhibitor is a compound of

formula 1:



FORMULA 1

wherein:

n is 1 or 2;

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R^1 is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, (substituted)phenyl, phenylalkyl, (substituted)phenylalkyl, heteroaryl, (heteroaryl)alkyl or $(CH_2)_mCO_2R^4$, wherein $m = 1-4$, and R^4 is as defined below;

R^2 is a hydrogen atom, chloro, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, (substituted)phenyl, phenylalkyl, (substituted)phenylalkyl, heteroaryl, (heteroaryl)alkyl or $(CH_2)_pCO_2R^5$, wherein $p = 0-4$, and R^5 is as defined below;

R^3 is a hydrogen atom, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenylalkyl, or (substituted)phenylalkyl;

R^4 is a hydrogen atom, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenylalkyl, or (substituted)phenylalkyl;

R^5 is a hydrogen atom, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenylalkyl, or (substituted)phenylalkyl;

A is a natural and unnatural amino acid;

B is a hydrogen atom, a deuterium atom, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, (substituted)phenyl, phenylalkyl, (substituted)phenylalkyl, heteroaryl, (heteroaryl)alkyl, halomethyl, CH_2ZR^6 , $CH_2OCO(aryl)$, $CH_2OCO(heteroaryl)$; or $CH_2OPO(R^7)R^8$, where Z is an oxygen or a sulfur atom;

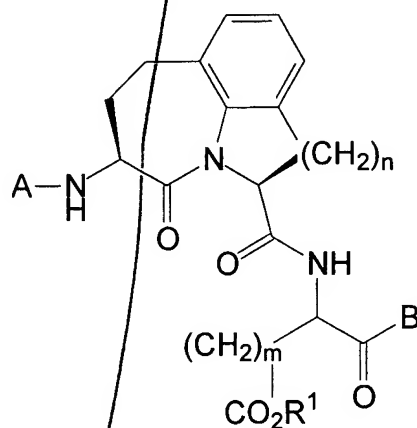
R^6 is phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, heteroaryl, or (heteroaryl)alkyl; and

R^7 and R^8 are independently selected from a group consisting of alkyl, cycloalkyl, phenyl, substituted phenyl, phenylalkyl, (substituted phenyl) alkyl, and (cycloalkyl) alkyl; and

X and Y are independently selected from the group consisting of a hydrogen atom, halo, trihalomethyl, amino, protected amino, an amino salt, mono-substituted amino, di-substituted amino, carboxy, protected carboxy, a carboxylate salt, hydroxy, protected hydroxy, a salt of a hydroxy group, lower alkoxy, lower alkylthio, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, (cycloalkyl)alkyl, substituted (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, and (substituted phenyl)alkyl;

or a pharmaceutically acceptable salt thereof.

16. The method of claim 12, wherein the protease inhibitor is a compound of formula 3:



FORMULA 3

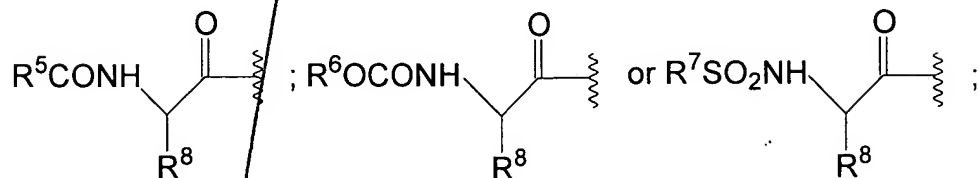
wherein:

n is 1 or 2;

m is 1 or 2;

A is R^2CO- , $R^3-O-CO-$, or R^4SO_2- ;

a group of the formula:



further wherein:

R^1 is a hydrogen atom, alkyl or phenylalkyl;

Subst
R² is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, phenylalkyl, substituted phenyl, (substituted phenyl)alkyl, heteroaryl, or (heteroaryl)alkyl;

R³ is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenylalkyl, or (substituted phenyl)alkyl;

R⁴ is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, phenylalkyl, substituted phenyl, (substituted phenyl)alkyl, heteroaryl, or (heteroaryl)alkyl;

R⁵ is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, phenylalkyl, substituted phenyl, (substituted phenyl)alkyl, heteroaryl, or (heteroaryl)alkyl;

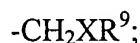
R⁶ is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenylalkyl, or (substituted phenyl)alkyl;

R⁷ is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, phenylalkyl, substituted phenyl, (substituted phenyl)alkyl, heteroaryl, or (heteroaryl)alkyl;

R⁸ is an amino acid side chain chosen from the group consisting of natural and unnatural amino acids;

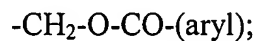
B is a hydrogen atom, a deuterium atom, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, phenylalkyl, substituted phenyl, (substituted phenyl)alkyl, heteroaryl, (heteroaryl)alkyl, or halomethyl;

a group of the formula:

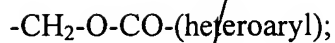


wherein R⁹ is phenyl, substituted phenyl, phenylalkyl, (substituted phenyl)alkyl, heteroaryl, or (heteroaryl)alkyl; and X is an oxygen or a sulfur atom;

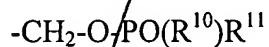
a group of the formula:



a group of the formula:

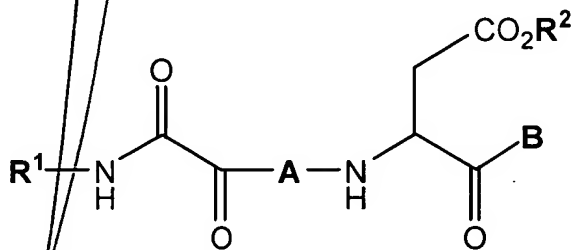


a group of the formula:



wherein R¹⁰ and R¹¹ are independently selected from a group consisting of alkyl, cycloalkyl, phenyl, substituted phenyl, phenylalkyl and (substituted phenyl) alkyl; and the pharmaceutically-acceptable salts thereof.

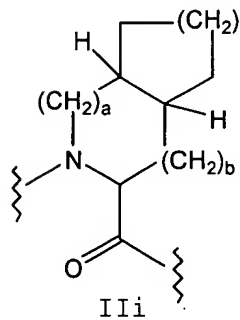
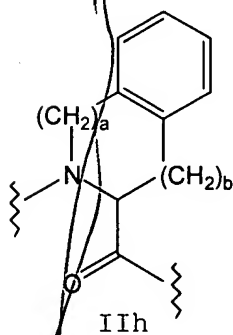
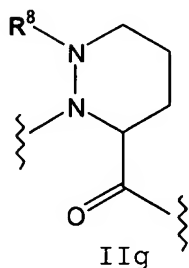
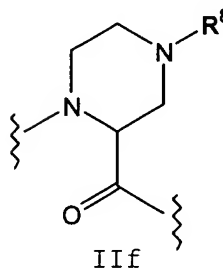
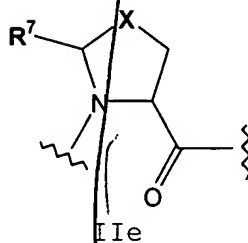
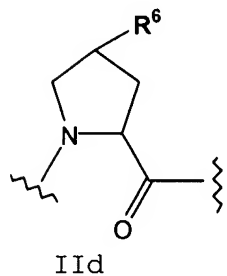
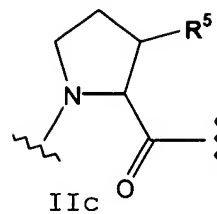
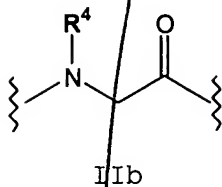
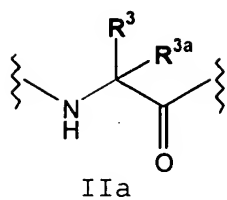
17. The method of claim 12, wherein the protease inhibitor is a compound of the formula:



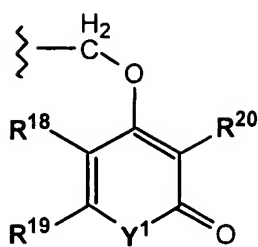
Formula I

wherein:

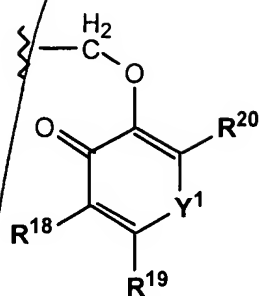
A is a natural or unnatural amino acid of Formula IIa-i:



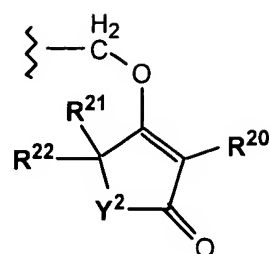
B is a hydrogen atom, a deuterium atom, C₁₋₁₀ straight chain or branched alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, 2-benzoxazolyl, substituted 2-oxazolyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), (CH₂)_n(heteroaryl), halomethyl, CO₂R¹², CONR¹³R¹⁴, CH₂ZR¹⁵, CH₂OCO(aryl), CH₂OCO(heteroaryl), or CH₂OPO(R¹⁶)R¹⁷, where Z is an oxygen or a sulfur atom, or B is a group of the Formula IIIa-c:



IIIa



IIIb



IIIc

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R^1 is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, heteroaryl, (heteroaryl)alkyl, $R^{1a}(R^{1b})N$, [or] $R^{1c}O$, 2-phenoxyphenyl or 2- or 3- benzylphenyl; and

R^2 is hydrogen, lower alkyl, cycloalkyl, (cycloalkyl)alkyl, phenylalkyl, or substituted phenylalkyl;

and wherein:

R^{1a} and R^{1b} are independently hydrogen, alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, heteroaryl, or (heteroaryl)alkyl, with the proviso that R^{1a} and R^{1b} cannot both be hydrogen;

R^{1c} is alkyl, cycloalkyl, (cycloalkyl)alkyl, phenyl, substituted phenyl, phenylalkyl, substituted phenylalkyl, naphthyl, substituted naphthyl, (1 or 2 naphthyl)alkyl, heteroaryl, or (heteroaryl)alkyl;

R^3 is C_{1-6} lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_nNH_2$, $(CH_2)_nNHCOR^9$, $(CH_2)_nN(C=NH)NH_2$, $(CH_2)_mCO_2R^2$, $(CH_2)_mOR^{10}$, $(CH_2)_mSR^{11}$, $(CH_2)_ncycloalkyl$, $(CH_2)_nphenyl$, $(CH_2)_n(substituted\ phenyl)$, $(CH_2)_n(1\ or\ 2-naphthyl)$ or $(CH_2)_n(heteroaryl)$, wherein heteroaryl includes pyridyl, thienyl, furyl, thiazolyl, imidazolyl,

pyrazolyl, isoxazolyl, pyrazinyl, pyrimidyl, triazinyl, tetrazolyl, and indolyl;

R^{3a} is hydrogen or methyl, or R^3 and R^{3a} taken together are $-(CH_2)_d-$ where d is an integer from 2 to 6;

R^4 is phenyl, substituted phenyl, $(CH_2)_m$ phenyl, $(CH_2)_m$ (substituted phenyl), cycloalkyl, or benzofused cycloalkyl;

R^5 is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ phenyl, $(CH_2)_n$ (substituted phenyl), or $(CH_2)_n$ (1 or 2-naphthyl);

R^6 is hydrogen, fluorine, oxo, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ phenyl, $(CH_2)_n$ (substituted phenyl), $(CH_2)_n$ (1 or 2-naphthyl), OR^{10} , SR^{11} or $NHCOR^9$;

R^7 is hydrogen, oxo, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ phenyl, $(CH_2)_n$ (substituted phenyl), or $(CH_2)_n$ (1 or 2-naphthyl);

R^8 is lower alkyl, cycloalkyl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ phenyl, $(CH_2)_n$ (substituted phenyl), $(CH_2)_n$ (1 or 2-naphthyl), or COR^9 ;

R^9 is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ phenyl, $(CH_2)_n$ (substituted phenyl), $(CH_2)_n$ (1 or 2-naphthyl), OR^{12} , or $NR^{13}R^{14}$;

R^{10} is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, $(CH_2)_n$ cycloalkyl, $(CH_2)_n$ phenyl, $(CH_2)_n$ (substituted phenyl), or $(CH_2)_n$ (1 or 2-naphthyl);

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R¹¹ is lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹² is lower alkyl, cycloalkyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹³ is hydrogen, lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, (CH₂)_ncycloalkyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or (CH₂)_n(1 or 2-naphthyl);

R¹⁴ is hydrogen or lower alkyl;

or R¹³ and R¹⁴ taken together form a five to seven membered carbocyclic or heterocyclic ring, such as morpholine, or N-substituted piperazine;

R¹⁵ is phenyl, substituted phenyl, naphthyl, substituted naphthyl, heteroaryl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), (CH₂)_n(1 or 2-naphthyl), or (CH₂)_n(heteroaryl);

R¹⁶ and R¹⁷ are independently lower alkyl, cycloalkyl, phenyl, substituted phenyl, naphthyl, phenylalkyl, substituted phenylalkyl, or (cycloalkyl)alkyl;

R¹⁸ and R¹⁹ are independently hydrogen, alkyl, phenyl, substituted phenyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl), or R¹⁸ and R¹⁹ taken together are -(CH=CH)₂-;

R²⁰ is hydrogen, alkyl, phenyl, substituted phenyl, (CH₂)_nphenyl, (CH₂)_n(substituted phenyl);

R²¹, R²² and R²³ are independently hydrogen, or alkyl;

X is CH₂, (CH₂)₂, (CH₂)₃, or S;

Y¹ is O or NR²³;

Y² is CH₂, O, or NR²³;

a is 0 or 1 and b is 1 or 2, provided that when a is 1 then b is 1;

c is 1 or 2, provided that when c is 1 then a is 0 and b is 1;

m is 1 or 2; and

n is 1, 2, 3 or 4;

or a pharmaceutically acceptable salt thereof.

Sub. a1